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Acute Kidney Injury in the Elderly: Predisposition to Chronic Kidney Disease and Vice Versa

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Key Words
Acute kidney injury · Aging · Chronic kidney disease · Glomerular filtration rate

Abstract
There have been considerable advances in the past few years in our understanding of how chronic kidney disease (CKD) predisposes to acute kidney injury (AKI) and vice versa. This review shows, however, that few studies have focused on the elderly or conducted stratified analysis by age. It does appear that elderly patients with estimated glomerular filtration rate (eGFR) 45–59 ml/min/1.73 m^2 are at higher risk for AKI compared with their counterparts with eGFR >60 ml/min/1.73 m^2. This is a similar relationship to that seen in younger patients, although effect size appears smaller. As the incidence of AKI has been increasing over the past several years, the proportion of elderly patients surviving after AKI has also been increasing. Since AKI heightens the risk for the development and acceleration of CKD, this implies significant public health concerns with regard to the absolute number of elderly persons developing incident CKD.

Introduction

Acute kidney injury (AKI) is particularly common among the elderly [1]. Pre-existing chronic kidney disease (CKD) is arguably the strongest risk factor for AKI [2]. Here, we review the recent literature on the relationship between AKI and CKD in elderly patients.

CKD and Predisposition to AKI

There has been considerable debate recently about the definition of 'chronic kidney disease' in elderly patients [see Winearls and Glassock, pp. c2–c4 this issue]. Doubts have been raised whether an estimated glomerular filtration rate (eGFR) cutoff of 60 ml/min/1.73 m^2 is appropriate to define CKD in all segments of the population, especially among the elderly, since there is a natural age-associated decline in renal function [3]. To inform this debate, one major thrust of active research in the CKD field is to better define the association between levels of eGFR and clinical outcomes [4]. To address the issue of CKD classification in the elderly, numerous papers have examined outcomes such as cardiovascular disease events (e.g. myocardial infarction or congestive heart failure) and mortality in age-stratified analyses [5–7].

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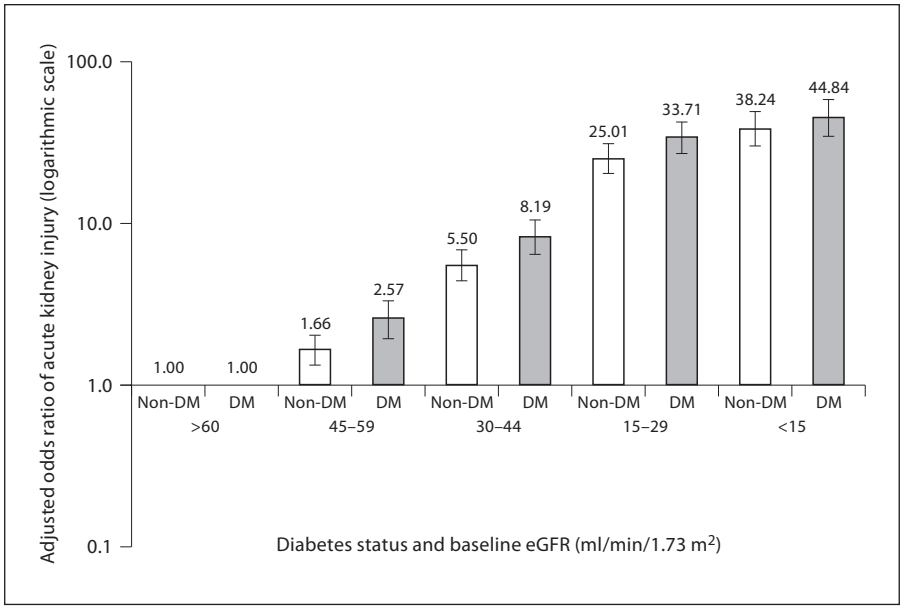

Fig. 1. Multivariable association of baseline eGFR and dialysis-requiring acute kidney injury stratified by the presence or absence of diabetes mellitus (DM) [modified from ref. 2].

However, until recently, no published study examined AKI as an outcome, even though a strong argument can be made that AKI compared to cardiovascular disease is more directly linked pathophysiologically to CKD. Therefore, any observed association between CKD and AKI is less likely to be due to confounding than analogous associations between CKD and cardiovascular disease [8].

A 2008 paper by Hsu et al. [2] quantified how risk of dialysis-requiring AKI varied by severity of preexisting CKD among a large cohort of patients receiving usual medical care in a Northern California integrated health care delivery system. That study found that an increase in risk of AKI becomes apparent starting below an eGFR of 60 ml/min/1.73 m^2. Even subjects with an eGFR 45–59 ml/min/1.73 m^2 have on average a two-fold increase in adjusted odds ratio of AKI compared with subjects with an eGFR of 60 ml/min/1.73 m^2 or above – with risk being higher among subjects with diabetes than among those without (fig. 1). These data support the *National Kidney Foundation Chronic Kidney Disease Guidelines* in which persons with eGFRs chronically below 60 ml/min/1.73 m^2 are classified as having CKD, regardless of other factors. Further age stratification analyses showed that the adjusted odds ratio was 2.73 (95% CI 2.12–3.51; $p < 0.0001$) for those aged ≤65 years, comparing patients with eGFR 45–59 ml/min/1.73 m^2 with their counterparts with eGFR ≥60 ml/min/1.73 m^2; for patients aged >65 years, the corresponding adjusted odds ratio was 1.33 (95% CI 1.08–1.64; $p = 0.008$) [unpubl. data].

A recent publication by Grams et al. [9] using data from the Atherosclerosis Risk in Communities (ARIC) Study obtained similar results. For example, the adjusted risk of AKI approximately doubled going from an eGFR of 60 to 45 ml/min/1.73 m^2. Interestingly, Grams et al., who used the CKD-EPI equation [10] to explore higher eGFR levels, reported that compared with those with eGFR 75 ml/min/1.73 m^2, relative hazards for AKI was nearly doubled in ARIC participants with eGFR of 60 ml/min/1.73 m^2. This is a stronger and earlier signal than that seen in numerous studies of eGFR and death or cardiovascular disease – where in some instances risk may not rise appreciably until eGFR is below 45 ml/min/1.73 m^2 [11–13]. This argues that the NKF threshold of an eGFR of 60 ml/min/1.73 m^2 may actually be too conservative in some clinical settings such as AKI. No age-stratified eGFR analysis was presented by Grams et al. [9].

In addition to a low eGFR, the other main manifestation of CKD is proteinuria and the importance of proteinuria in the classification of CKD has received much attention recently. Hsu et al. [2] first reported that proteinuria is an important independent risk factor for AKI. Patients with documented dipstick proteinuria appear to be 2–3 times as likely as patients without it to develop AKI, independent of eGFR. Grams et al. [9] further quantified a graded relationship between severity of proteinuria (albuminuria) and risk of AKI. With participants who had

urine albumin-to-creatinine ratios <10 mg/g as a reference, the adjusted hazards ratios of AKI were 1.9, 2.2, and 4.8 for urine albumin-to-creatinine ratio groups of 11–29, 30–299 and ≥300 mg/g, respectively. Age-stratified analysis showed that the associations between crude rates of AKI and severity of baseline albuminuria were similar in those above or below age 65 years (fig. 2).

Several other recent studies have also concluded that proteinuria is a risk factor for AKI in the setting of cardiac catheterization [14], cardiac surgery [15] and in the general population [16]. But no comparisons of older and younger patients were reported.

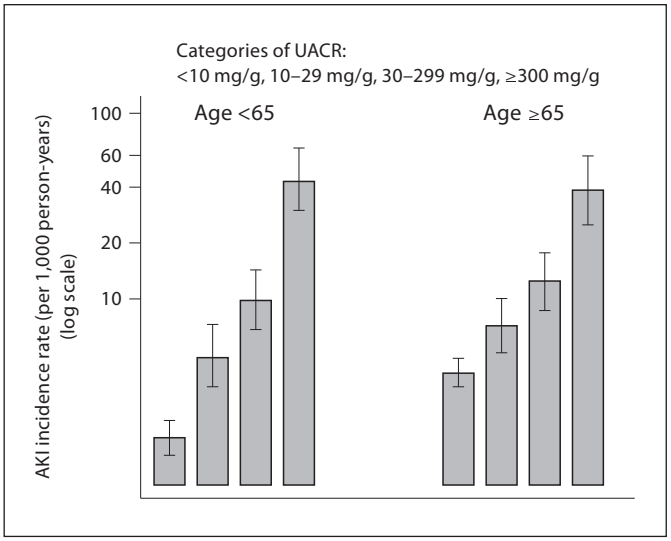

Fig. 2. Incidence rates of acute kidney injury by level of baseline albuminuria, stratified by age above or below 65 years [modified from ref. 9]. UACR = Urine albumin-to-creatinine ratio.

AKI and Predisposition to CKD

A plethora of data over the past several years, both from experimental studies in animals and from human studies, indicates that AKI not infrequently leads to CKD.

In experimental animals, a robust fibrotic response in the kidney is apparent several days to weeks after a single episode of AKI induced by ischemia-reperfusion injury [17, 18]. This fibrotic response is enhanced by older age [19]. The primary mediator of this relationship is multifactorial, implicating microvascular damage [17], increased sensitivity to angiotensin II [20] and upregulation of genes associated with inflammation, remodeling and fibrosis [21, 22]. In aged mice, expression of zinc-α_2-glycoprotein may influence the exaggerated fibrotic response [19]. A significant manifestation of the post-AKI injury phenotype is salt-sensitive hypertension [23, 24].

The preponderance of evidence from epidemiologic studies supports the notion that AKI leads to CKD in elderly persons. First, older age is associated with a greater chance of nonrecovery of renal function back to baseline after AKI by the time of hospital discharge [25]. Second, several studies have demonstrated that even after adjustment for several important covariates, AKI is independently associated with an increased risk for both CKD and end-stage renal disease (ESRD) (table 1). In elderly patients, the risk for ESRD after a single episode of AKI is elevated 2-fold in those with mild AKI [26], and elevated by 3- to 13-fold in those with more severe AKI [16, 26–28]. The annual absolute risk for developing ESRD is approximately 0.6–1.2% after mild AKI [14, 26], but 1.7–2.9% after severe AKI [14, 26–28]. The annualized risk of ESRD increases to 7–9% if the AKI occurs in an individual with a preexisting history of CKD [16, 27, 28]. The *relative risk* for ESRD may [28] or may not [27] be higher in those of older age (vs. younger age) after AKI. If the latter is true (lower relative risk of ESRD with older age vs. younger age), the effect is likely confounded by the competing risk of death.

ESRD only represents the most severe manifestation of CKD. Less severe stages of CKD are still associated with a markedly increased risk of cardiovascular disease, poorer quality of life and increased health care costs [11]. The incidence rate of CKD (stage 4 or worse) is approximately 120 per 1,000 person-years after non-dialysis-requiring AKI [29] and 479 per 1,000 person-years in those who required dialysis for AKI [30]. These absolute incidence rates are commensurate with adjusted hazard ratios of at least 4 for non-dialysis-requiring AKI and 28 for dialysis-requiring AKI (compared to no AKI, respectively) [29, 30].

In a recent study examining the rate of eGFR decline in patients undergoing cardiac catheterization, James et al. [14] demonstrated that the rate of decline in eGFR was 1.0 ml/min/1.73 m^2 per year after mild AKI and 2.8 ml/min/1.73 m^2 per year after moderate or severe AKI (compared with 0.1 ml/min/1.73 m^2 per year in those without AKI). Although these rates were adjusted for age (along with proteinuria and comorbidities), it is unclear whether older age was associated with a more rapid decline of eGFR, as would be hypothesized based on data from experimental animals. Factors that clearly modify the effects of the relationship between AKI and progressive CKD are level of baseline renal function and degree of

Table 1. Adjusted rate ratios for ESRD or doubling of serum creatinine by baseline kidney function and proteinuria

Study	Setting	Patients n	AKI definition	ESRD		Comments
				incidence rate person-years	adjusted HR	
Amdur et al. [29]	hospitalized veterans	113,272	ICD-9 codes ATN ARF controls (no AKI) CKD without AKI	 20.0%[a] 13.2%[a] 3.3%[a] 24.7%[a]	 6.64[a] 4.03[a] 1.0[a] 6.5[a]	mean ages by group, years 63.8 66.5 68.7 74.4 No age-specific analyses reported
Hsu et al. [34]	hospitalized with pre-existing CKD	39,805	acute dialysis	12.7% at 6 months	1.47 (0.95–2.28)	mean age 66.6 years in those with AKI no age-specific analyses reported
Ishani et al. [27]	Medicare	233,803	ICD-9 based: AKI AKI on CKD	 27.5/1,000 101.5/1,000	 13.0 (11.0–16.0) 41.2 (34.6–49.1)	incidence rate; adjusted HR for ESRD by age strata (total population; not by AKI/no AKI) age, years: 67–70: 8/1,000; 1.0 71–75: 6.9/1,000; 0.87 (0.74–1.02) 76–80: 5.7/1,000; 0.72 (0.61–0.85) 81–85: 4.3/1,000; 0.63 (0.52–0.76) ≥ 86: 1.9/1,000; 0.36 (0.28–0.46)
Lo et al. [30]	population-based cohort	3,773	in-hospital dialysis vs. matched non-AKI	479/1,000[b] 17/1,000[b]	28.1 (21.1–37.6)[b]	mean age of AKI 63.5 no age-specific analyses reported
Newsome et al. [26]	Medicare-Acute MI	87,094	change in SCr: None Cr ↑ 0.1 Cr ↑ 0.2 Cr ↑ 0.3–0.5 Cr ↑ 0.6–3.0	 2.3/1,000 2.3/1,000 3.6/1000 6.3/1,000 20.0/1,000	 1.0 1.45 1.97 2.36 3.26	entire cohort was aged ≥67 no age-specific analyses reported
Wald et al. [28]	population-based cohort	17,367	in-hospital dialysis vs. matched non-AKI	26/1,000 9/1,000	3.23 (2.7–3.86)	absolute risk and excess risk for ESRD after AKI higher in patients aged ≥65 (AKI 9.5% vs. non-AKI 2.8%) compared to those aged <65 (7.4 vs. 3.2%)
James et al. [14]	coronary angiography	11,249	no AKI mild AKI moderate/severe AKI	3.7%[c] 9.4%[c] 21.8%[c]	1.0 1.60 (1.19–2.14) 3.12 (1.95–4.99)	mean age 67 in those with AKI no age-specific analyses reported
James et al. [16]	population-based cohort	920,985	AKI (ICD-9 and -10) vs. no AKI	3.5/1,000[d] 0.78/1,000[d]	21–230, depending on baseline GFR and degree of proteinuria	no age-specific analyses reported

Figures shown in parentheses are 95% CI. ATN = Acute tubular necrosis; ARF = acute renal failure.

[a] Cumulative incidence at 20% percentile follow-up of 10.9 months in ATN and 57 months in ARF. [b] Endpoint was CKD stage 4 or higher.

[c] Cumulative incidence with median follow-up of 21 months for composite endpoint of decline in eGFR >4 ml/min/1.73 m^2 or ESRD. [d] Endpoint was ESRD or doubling of serum creatinine (SCr).

proteinuria [16]. The risk for progressive CKD attributable to AKI attenuates with lower levels of baseline eGFR and higher levels of proteinuria.

With regard to public health, approximately 40 million people in the US are aged ≥65 in 2010. Since the incidence of AKI in this elderly population is approximately 3,000 per 100,000 person-years [1] and 75% will survive to discharge after AKI, and the incidence of stage 4 or worse CKD after AKI is approximately 120 per 1,000 person-years [estimated from Kaplan-Meier curve in figure 3 of reference 29] then approximately 100,000 elderly persons per year in the United States are developing new CKD after an episode of AKI. Clearly, the challenges for the nephrology community are to find strategies to either

prevent AKI or prevent the transition from AKI to CKD. Until these strategies are developed and proven to be effective, CKD and ESRD after AKI in elderly patients represent a substantial public health burden.

Conclusion

In summary, elderly patients with eGFR 45–59 ml/min/1.73 m^2 are at higher risk for AKI compared with their counterparts with eGFR >60 ml/min/1.73 m^2. This is a similar relationship to that seen in younger patients, although effect size appears smaller. As the incidence of AKI has been increasing over the past several years [1], the proportion of elderly patients surviving after AKI has also been increasing [31–33]. Since AKI heightens the risk for the development and acceleration of CKD, this implies significant public health concerns with regard to the absolute number of elderly persons developing incident CKD.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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